Applicants: Graham P. Allaway et al.
Serial No.: 09/904,356
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**Exhibit 26**

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JOHN P. WHITE
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# PCT

## NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>43966-C-PCT | Date of Mailing *(day/month/year)*<br>05 SEP 1997 |
| | IMPORTANT NOTIFICATION |

| International application No. | International filing date *(day/month/year)* | Priority Date *(day/month/year)* |
|---|---|---|
| PCT/US96/09894 | 07 JUNE 1996 | 07 JUNE 1995 |

Applicant
PROGENICS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| | |
|---|---|
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>JEFFI |
| Facsimile No. (703) 305-3230 | Telephor |

Form PCT/IPEA/416 (July 1992)*

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference<br>43966-C-PCT | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/US96/09894 | International filing date *(day/month/year)*<br>07 JUNE 1996 | Priority date *(day/month/year)*<br>07 JUNE 1995 |
| International Patent Classification (IPC) or national classification and IPC<br>IPC(6): C12Q 1/70; G01N 33/53, 33/555, 33/567 and US Cl.: 435/5, 7.1, 7.2, 7.24, 7.8 | | |
| Applicant<br>PROGENICS PHARMACEUTICALS, INC. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 23 DECEMBER 1996 | 11 AUGUST 1997 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>for<br>JEFFREY S. PARKIN, PH.D.<br>Telephone No. (703) 308-0196 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US96/09894

## I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-64 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-6 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-5 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US96/09894

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. STATEMENT

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-6 | YES |
| | Claims | NONE | NO |
| Inventive Step (IS) | Claims | NONE | YES |
| | Claims | 1-6 | NO |
| Industrial Applicability (IA) | Claims | 1-6 | YES |
| | Claims | NONE | NO |

2. CITATIONS AND EXPLANATIONS

Claims 1-6 lack an inventive step under PCT Article 33(3) as being obvious over the combined teachings of Dimitrov *et al.* (1991), Sinangil *et al.* (1988), Chams *et al.* (1992), Szabo *Jr. et al.* (1992), Peden *et al.* (1991), and Fouchier *et al.* (1994).

Dimitrov *et al.* (1991) describe an HIV-1 envelope glycoprotein-mediated cell fusion/syncytal formation assay based upon the redistribution of fluorescent dyes. The authors reported the following concerning the development of this assay (refer to **ABSTRACT**, page 799):

> To gain insight into mechanisms of HIV *env*-mediated membrane fusion, we developed a new assay for studying the initial events. The assay is based on the redistribution of fluorescent markers between membranes and cytoplasm of adjacent cells examined by means of fluorescence video microscopy. Membrane fusion between HIV-1 envelope glycoprotein (gp120/41) expressing effector cells and $CD4^+$ target cells was observed 90 min after the association of cells, whereas the first syncytia only became apparent after 5 h. Moreover, membrane fusion events were observed under conditions where no syncytia were detected, for example, when the effector:target cell ratio was greater than 100:1, or less than 1:100.

The authors disclose cell lines expressing CD4, HIV-1 Env, and suitable fluorophores (refer to **MATERIALS AND METHODS**, page 800).

Sinangil *et al.* (1988) teach methods employing membrane fluorescence dequenching to quantitatively measure fusion between the HIV-1 Env and target cell membranes. The requisite reagents (i.e., $CD4^+$ and $CD4^-$ cell lines, HIV-1 Env, and fluorophores (e.g., octadecylrhodamine B-chloride (R-18)) and methods (i.e., fluroescence measurements and quantitation) were disclosed on page 89 (refer to **MATERIALS AND METHODS**). The authors conclude (refer to DISCUSSION, page 91) that "The results presented here demonstrate the application of membrane fluorescence dequenching technique [17] to a quantitative measurement of the process of HIV penetration into target cells."

Chams *et al.* (1992) teach the generation of an enzyme-linked immunosorbent assay (ELISA) which detects interactions between

(Continued on Supplemental Sheet.)

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
recombinant soluble forms of CD4 (rsCD4) and HIV-1 gp160. This assay is clearly useful for the identification of anti-viral agents capable of abrogating this interaction. The authors identified a number of compounds capable of inhibiting this interaction including antibodies and rsCD4 (refer to Figure 1 and Table 1, page 269). It was further emphasized by the authors that (refer to DISCUSSION, pages 270-271):

> The interaction of HIV gp120 with the CD4 receptor is an important target for the development of anti-HIV therapeutic agents. Several groups of investigators have generated sCD4 as well as several sCD4 derivatives that inhibit this interaction. In addition to this rational therapeutic design, it is also important to perform empirical screening of libraries of synthetic chemical compounds and natural products to identify inhibitors of the HIV gp120-CD4 interaction. In this regard, we developed a series of three complementary assays to identify anti-HIV compounds.

This teaching clearly describes the clinical import of developing rational anti-viral drug screening methodologies.

Szabo *Jr. et al.* (1992) performed photobleaching fluorescence resonance energy transfer (pFRET) measurements to examine binding interactions between HIV-1 gp120 and CD4. The authors identified a therapeutic compound (e.g., aurintricarboxylic acid or ATA) that precludes HIV-1 gp120 binding to CD4 (refer to ABSTRACT, page 3596).

Peden *et al.* (1991) describe the biological characterization of three infectious molecular clones of HIV-1, designated LAI, MAL, and ELI, on different cell types including peripheral blood mononuclear lymphocytes (PBMCs), promonocyte cell lines, and established T-cell lines (refer to RESULTS, pages 664-665). The isolate MAL is representative of monocyte/macrophage-tropic isolates.

Fouchier *et al.* (1994) teach the importance of macrophage tropic HIV-1 isolates in AIDS pathogenesis. The ability of 19 primary virus isolates to infect monocyte-derived macrophages (MDM) from different seronegative donors was assessed using standard biochemical and virological techniques (refer to **Methods**, pages 1806-1807 and Figure 1, page 1807). In addition to the primary isolates, the authors also employed the previously characterized macrophage-tropic isolates HIV-1-Ba-L and HIV-1-ACH-172.Ba-L. It was further reported that the predominance of HIV-1 macrophage-tropic isolates during the asymptomatic period and their presence throught all stages of infection illustrate their importance in viral persistence.

The prior art can be summarized as follows:

1) Fluorescence resonance energy transfer (FRET) HIV *env*-mediated membrane fusion assays were routinely employed in the art to study membrane fusion between HIV-1 envelope glycoprotein (gp120/41) expressing effector cells and $CD4^+$ target cells.
2) Compounds (e.g., antibodies, rsCD4, rsCD4-based derivatives) capable of inhibiting HIV-1 Env-CD4 interactions are taught.
3) The clinical import of performing empirical screening assays

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



using libraries of synthetic chemical compounds and natural products to identify inhibitors of the HIV gp120-CD4 interaction is disclosed.
4) The genotypic and phenotypic properties, as it applies to cell-tropism and as modulated by the *env* gene, of numerous HIV isolates were well known.
5) The import of macrophage-tropic isolates in the clinical sequelae leading to AIDS was disclosed.
When the aforementioned factors are considered *in toto*, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to employ art-recognized FERT assays to identify putative therapeutics capable of abrogating macrophage-tropic HIV-1 Env-CD4 binding interactions.

---------- NEW CITATIONS ----------

SINANGIL et al. Quantitative measurement of fusion between human immunodeficiency virus and cultured cells using membrane fluorescence dequenching. FEB Vol. 239, Number 1, October 1988, pages 88-92, see entire document.

SZABO JR., et al. CD4 changes conformation upon ligand binding. J. Immunol Vol. 149, 1992, pages 3596-3604, see entire document.

PEDEN et al. Changes in growth properties on passage in tissue culture of viruses derived from infectious molecular clones of HIV-1LAI, HIV-1MAL, and HIV-1ELI. Virol Vol. 185, 1991, pages 661-672, see entire document.